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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/905,452
Filing Date: July 13, 2001
Appellant(s): NASIR ET AL.

Richard A. Machonkin
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed February 2, 2006 appealing from the Office action mailed August 24, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

1.Declaration of Mohammad S. Nasir Pursuant to 37 C.F.R. 1.132

2. Pestka et al, "Immunological Assays for Mycotoxin Detection", Food Technology, February 1995, pp. 120-128

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-4 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable Dixon et al (USP#4,835,100) in view of Nasir et al (Combinatorial Chemistry & High Throughput Screening, 1999, 2, 177-190).

Dixon et al teaches a method and a test kit for detecting an aflatoxin B1 using monoclonal antibodies (See abstract and column 3, lines 16-19). The antigens or antibodies to aflatoxins are conjugated to a label (see abstract) and more specifically, horseradish peroxidase (column 6, lines 34-37) and BSA (column 5, lines 12-14). Dixon et al explains that aflatoxin B1 is converted to aflatoxin B1-oxime for labeling (column 4, lines 62-68 and column 5, lines 1-15). Dixon et al explains that aflatoxins are toxic metabolites and they can act as potent carcinogens, mutagens and teratogens and are known to occur naturally in wheat and other foods (col. 1, lines25-34) and (col. 10, lines 45-52). Dixon et al uses methanol as an extraction solvent (col. 11, lines 36-47). ELISA assay methods were used for detection of aflatoxins (column 7, lines 1-5).

The reference of Dixon does not teach the detection of aflatoxins in a Fluorescent Polarization Assay format, however, Nasir et al teaches field tests to determine mycotoxins (a form of aflatoxins) in human, animal and grain diseases. (pg. 18, last para.). Nasir et al teaches a homogenous assay using fluorescence polarization to analyze these mycotoxins in grains (See abstract). Mycotoxins that are extracted from grains, with a suitable solvent and the sample are added into the antibody solution. A mycotoxin antigen of interest is labeled with a fluorescent molecule

(tracer) and is added to the antibody solution. Once the reaction takes place, the fluorescent polarization of the tracer is then measured (pg. 182, para. 1). Nassir et al also teaches that using fluorescent polarization assays has good sensitivity and the possibility of obtaining results rapidly without any separation and purification steps make Fluorescent Polarization more attractive than methods where one needs to physically separate the bound and unbound species before analysis.

Therefore, it would have been obvious to one of ordinary skill in the art to modify the reference of Dixon et al to detect aflatoxins utilizing Fluorescent Polarizations assay as taught by Nasir et al because this type of assay is sensitive and results can be obtained rapidly without any separation and purification steps. One would be motivated because detect a variety of forms of mycotoxins which includes aflatoxins because they are known toxins found in grains and can pose health risks.

Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dixon in view of Nasir et al, and further in view of and further in view of Michel et al (USP#5,741,654).

The teachings of Dixon et al in view of Nasir et al are set forth above and differ from the instant claims in not particularly pointing out a particular type of fluorescein used in the assay.

However, Michel et al discloses a Fluorescence Polarization assay for the quantification of antibodies in which a variety of fluoresceins are used as detectable moiety components of tracers, such as one mentioned in particular, the

6-aminofluorescein moiety (isomer II of fluorescein) which is one of the preferred moieties of choice in the said assay (col. 8, lines 1-22).

It would have been obvious to one of ordinary skill in the art to employ a fluoresceinamine or its isomers as binding moieties because such structures are well known in the art to work well in Fluorescence Polarization Immunoassays for quantitation of a sample. In addition, the fluorescein used for labeling in this assay would have been a functional equivalent of the fluorescent molecule used for labeling in the assay of Dixon et al in view of Nasir et al - wherein both would have worked equally as well absent unexpected results.

Claims 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dixon et al in view of Nasir et al and further in view of McMahon et al (USP#5,166,078).

The teachings of Dixon et al in view of Nasir et al are set forth above and differ from the instant claims in not teaching the construction of a standard curve using a plurality of different known concentrations of aflatoxin.

However, McMahon et al teaches a method for measuring a hapten that is poorly soluble in an aqueous solution such as aflatoxins (col. 2, lines 45-53). The invention permits fast, safe, and convenient measurements of haptens, which are either insoluble or unstable in aqueous solution by providing standards that are soluble and stable in aqueous solution. The standards are used to determine the amount of haptens that are present in the assay (col. 1, lines 43-48). To determine the amount of hapten in a sample, the reaction of the hapten and the antibody is compared to the reaction of the

hapten-conjugate and the antibody. The conjugates of the invention are used as controls in standard immunoassay (col. 2, lines 29-40). The reactivity of the conjugate was compared to aflatoxin standards and a standard curve was created relating aflatoxin levels to aflatoxin-conjugate levels (col. 3, lines 9-16).

It would have been obvious to one of ordinary skill in the art to use a plurality of aflatoxins in standard solutions having different known concentrations and comparing them with aflatoxin-conjugates to create a standard curve to permit fast, safe and convenient measurements of haptens. Further, one skilled in the art would know that certain levels of aflatoxins found in different amounts of grain are toxic to human and animals and a standard curve is needed to compare those levels that would be of concern.

Claims 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nasir et al in view of Dixon et al.

The teachings of Nasir et al are set forth above and differ from the reference of Dixon in not teaching a kit.

However, Dixon et al however discloses a kit for afltoxins and explains that obvious variations of preparing a kit for convenience will be apparent to those skilled in the art and points out that kits are well developed in the patent arts and literature (col. 12, lines 28-33).

It would have been prima facie obvious to one of ordinary skill in the art to take the assay for aflatoxins as taught by Dixon et al, combined with the teachings of Nasir et

and formulate a kit. Further, it would be convenient to do so because one can enhance sensitivity of a method by providing reagents as a kit. In addition, the reagents in a kit are available in premeasured amounts, which eliminates the variability that can occur when performing the assay.

(10) Response to Argument

Patentability of Group I, Claims 1-4, 8 and 11-18

Applicant's argument No. 1 on page 3 have been considered but not found to be persuasive. In response, the reference of Dixon teaches an ELISA for detecting aflatoxin oxime conjugated to the enzyme horse radish peroxidase (Dixon, col. 6, lines 34-37).

Applicant's argument No. 1a. on pages 4-5 have been considered but not found to be persuasive. In response, the reference of Nasir teaches a Fluorescence Polarization assay for detection of mycotoxins, which is a form of aflaxotins. The reference of Dixon discloses that aflatoxins does not possess reactive groups for conjugation of labels, therefore it has to be first converted to aflatoxin B1-oxime before being conjugated to a label (Dixon column 4, lines 62-68). Therefore, the reference of Nasir is not teaching away from the instant claimed invention. In essence, the reference of Nasir alone suggests independent claims 1 and 11 by teaching a Fluorescence Polarization assay for detection of Mycotoxins, which is a form of aflatoxins. And since aflatoxins has to first be converted to an aflatoxin oxime before being conjugated to a

label, Nasir would have had to perform this method before detection of aflatoxins using the method of Fluorescence Polarization.

However, the primary reference of Dixon was combined with Nasir because Dixon actually taught detection of aflatoxin oxime with an ELISA assay. The Nasir reference modifies Dixon by teaching a Fluorescence Polarization assay and its benefits of sensitivity and results can be obtained rapidly without any separation and purifications steps. Although Nasir didn't name all the species of mycotoxins that was detected with Fluorescence Polarization, however, Nasir, would have wanted to detect a broad range of mycotoxins, which includes detection of aflatoxins because they are known toxins found in grains and can pose health risks. Therefore, Nasir, using a Fluorescence Polarization assay would have had to conjugate a fluorophore to the aflatoxins detected. With respect to applicant arguing the reference of Dixon in view of Nasir separately, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). With respect to the case law recited by applicant, the modification of Dixon by Nasir would not change the principle operation of the prior art invention because both references are drawn to detection of toxins in grains. Therefore, the principle of operation appears to be the same.

Applicant's argument No.1b.on page 6 have been considered but not found to be persuasive. In response, the reference of Dixon taught that aflatoxin B1 does not

possess the properties for conjugation and therefore has to be converted to aflatoxin B1 oxime. Dixon teaches the labeling of aflatoxin B1 oxime, which involves antibody buinding. Therefore it would appear that Nasir would have a reasonable expectation of success in modifying the reference of Dixon to include detection of aflatoxins utilizing a fluorescence polarization assay. Applicant's argument with respect to Dixon and Nasir not being properly combined and the references teach away from their instant combination have been considered but not found to be persuasive. In response, these arguments have been addressed above (see arguments for page 1).

Applicant's argument No 2 on page 7 have been considered but not found to be persuasive. In response, although the prior art reference does not teach an aflatoxin oxime conjugated to a flourophore label, the prior art does however teach an aflatoxin oxime conjugated to a horse radish peroxides label. Nasir taught using a Fluorescence Polarization assay method to label and detect a broad range of mycotoxins, which is a form of aflatoxins. Dixon has already established in the art that aflatoxins does not possess reactive groups for conjugation of labels and therefore must first be converted to aflatoxin B1-oxime before being conjugated to a label (Dixon col. 4, lines 62-68). The reference of Dixon taught detection of aflatoxin oxime with an ELISA assay that included antibody binding successfully to aflatoxin oxime. Therefore, the prior art teaches that afltoxin oxime can be successfully be detected and bound to antibodies. Although applicant argues that Nasir describes a phenomenon called "propeller effect" which describes that binding have occurred but little polarization is observed and is

caused by the uncoupling of the flouorophore is not found persuasive. In response, Nasir overcame this obstacle by modifying the linkage between the fluorophore and the mycotoxin, as applicant also acknowleged (Nasir page 9, paragraph 1). Therefore, one of ordinary skill in the art would have wanted to detect toxins in grain, namely aflatoxins using FP because it offers sensitive results that can be obtained rapidly without any separation and purification steps.

Patentability of Group 2, Claims 5-7

Applicant's argument No. 2B on page 10 I have been fully considered but not found to be persuasive for reasons that have been addressed above.

Patentability of Group 3, Claims 9-10

Applicant's argument No. 2C on page 10 have been fully considered but not found to be persuasive for reasons that have been addressed above.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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